PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Urban scaling of opioid overdose deaths in the United States: a cross-sectional study in three periods between 2005 and 2017.
AUTHORS	Mullachery, Pricila; Lankenau, Stephen; Diez Roux, Ana V.; Li, Ran; Henson, Rosie Mae; Bilal, Usama

VERSION 1 – REVIEW

REVIEWER	Jennifer Ellis Johns Hopkins University
REVIEW RETURNED	20-Mar-2021

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript, entitled "Urban scaling of opioid overdose deaths in the United States: a cross-sectional study in three periods between 2005 and 2017". The purpose of the present study was to explore relationships between age-adjusted opioid overdose death rates and both population size and growth. Results indicated that larger commuting zones had a higher rate of overdose mortality, and that this was particularly true among areas with population decline. Scaling of opioid deaths differed by the type(s) of opioid involved in the death. There are several strengths associated with this study. First, the examination of how population growth in relation to opioid overdose deaths is interesting and novel. Another exciting aspect of the study is the interactive web app that allows the reader to more fully visualize and explore the results. The authors also include rich supplemental material that is helpful in interpreting and understanding the results. Finally, the manuscript is extremely well-written. I have a couple of questions and recommendations: 1) In the introduction, it would be helpful if the authors could expand on the literature that they review on population growth/decline. The authors note that other health outcomes have been linked to population growth or decline; I am curious what these outcomes were and how these studies informed the present work. 2) It is recommended that the authors state whether they formed specific hypotheses about whether they expected to see superlinear or sublinear scaling for opioid overdose, and how they expected population change to influence overdose. From the introduction it is unclear whether they expected population growth to be associated with higher or lower overdose rates. 3) I recommend citing previous work (i.e., Rudd, Aleshire, Zibbell, & Gladden, 2016; Gomes et al., 2018) or providing a more complete

	rationale when describing the decision to include self-poisoning and homicidal poisoning in drug-overdose death rates along with explicit accidental opioid overdose. The coding utilized by the authors is consistent with previous work, but may at first appear counterintuitive to readers. 4) I agree with the authors that one limitation with the present analysis is that deaths with more than one contributory code were included in more than one sub-analysis, and should be interpreted with caution. Would it be possible to include secondary analyses to see how robust the findings are when multiple-opioid deaths are excluded vs. included? For example, in the online tool, rather than having to choose between 3 drug types, would there be a way to set this up that the viewer can “select all drugs that apply”. In this way, viewers could see how the results change for “prescription opioid only” deaths vs. “heroin and prescription opioid deaths”. 5) Another limitation of the present analysis is that 25% of drug-poisoning deaths were coded as unspecified. I appreciate the authors discussing how analyses change before and after imputation. I would also be curious to know whether specific CZ codes or geographic regions were particularly likely to have unspecified drug-poisoning deaths. If so, this may be helpful to note. 6) A very brief explanation of the rationale for using a binary logarithm of the average population in the text would be helpful. 7) It appears that higher CZ deciles have more variability in the most recent time period relative to the smaller population deciles and earlier years. This may be an interesting discussion point to raise and a direction for future research (for example, what contributes to variability in opioid mortality rates within the high-risk decile, beyond population decline?) 8) In the limitations section, the authors state that broader social determinants of health and factors in the local content have a role in the development of substance use disorders. I may recommend changing “substance use disorders” to “overdose” more specifically, as overdose was the focus of the present analysis and because an individual without a substance use disorder can overdose. 9) In the following sentence of the limitation sections, the authors generally refer to and recommend harm reduction strategies; more specific recommendations tied to the results of the present study would be beneficial. For example, the authors note that superlinear scaling of opioid deaths was largely driven by synthetic opioids, consistent with rising fentanyl in the drug supply. Increasing access to fentanyl testing strips and naloxone may be actionable harm reduction strategies that the authors could discuss in light of the their findings. 10) Additionally, it is recommended that the authors raise limitations associated with death codes generally, such as varied investigation systems by state, and incomplete toxicology testing in some jurisdictions. While the authors elude to this in the limitations section, a slightly expanded discussion is recommended.

REVIEWER	Katherine Jones East Carolina University, Public Health
REVIEW RETURNED	09-Apr-2021

GENERAL COMMENTS	This paper is clear and well written. It presents an analysis to describe the relationship between US urban population size and population growth, and opioid-related mortality. This analysis finds a relationship between urban population decline and higher rates of opioid-related mortality. It does not establish a cause for the relationship. The use of commuting zones is novel, and a good addition to the study of geographic variability in opioid-related mortality. I have not reviewed the statistical methods as this is outside of my area.

REVIEWER	Kavita Batra University of Nevada Las Vegas
REVIEW RETURNED	02-Nov-2021

GENERAL COMMENTS	Authors did an excellent job in describing the statistical approach to allow replication. Best wishes,

VERSION 1 – AUTHOR RESPONSE

Reviewer 1	
Thank you for the opportunity to review this manuscript, entitled “Urban scaling of opioid overdose deaths in the United States: a cross-sectional study in three periods between 2005 and 2017”. The purpose of the present study was to explore relationships between age-adjusted opioid overdose death rates and both population size and growth. Results indicated that larger commuting zones had a higher rate of overdose mortality, and that this was particularly true among areas with population decline. Scaling of opioid deaths differed by the type(s) of opioid involved in the death. There are several strengths associated with this study. First, the examination of how population growth in relation to opioid overdose deaths is interesting and novel. Another exciting aspect of the study is the interactive web app that allows the reader to more fully visualize and explore the results. The authors also include rich supplemental material that is helpful in interpreting and understanding the results. Finally, the manuscript is extremely well-written. I have a couple of questions and recommendations:	Thank you for your thoughtful review and the many helpful and specific comments on how to improve this paper. We really appreciate your time. Below, we described the changes made in the paper.
1) In the introduction, it would be helpful if the authors could expand on the literature that they review on population growth/decline. The authors	Thank you for highlighting this important issue. In the new version we expanded the paragraphs discussing the literature on population growth and

note that other health outcomes have been linked to population growth or decline; I am curious what these outcomes were and how these studies informed the present work.	health outcomes. "Additionally, while most studies on scaling have used population size as the main exposure, recent reports have also examined population growth. For example, UK districts that have shrunk over time have higher age-standardized mortality[1] while Latin American cities with higher population growth have higher life expectancy.[2] Population growth can be thought of as a cause of improved living conditions, for example through the demographic dividend, i.e., when the share of the working-age population is larger than the non-working-age share of the population,[3] or as a consequence of it, as increases in population can result from changes in economic opportunities, with economically strong areas attracting people from other regions.[4] Growing areas may be receiving more migrants, which tend to have improved health status,[5] causing at least in part these growth-mortality associations.[6]"
2) It is recommended that the authors state whether they formed specific hypotheses about whether they expected to see superlinear or sublinear scaling for opioid overdose, and how they expected population change to influence overdose. From the introduction it is unclear whether they expected population growth to be associated with higher or lower overdose rates.	We had a working hypothesis in previous versions but decided to remove from the final version. We have now added the hypothesis back. "We hypothesized that a large number of contacts resulting from larger population counts will be associated with a disproportionally higher count of opioid deaths (superlinear scaling) due to a increase in successful matches between susceptible people and sources of prescription and illicit opioids.[7] The relationship between population growth and opioid mortality may be inverted, as population growth can be an indicator of communities with a thriving economy and potentially lower rates of mortality.[8-10]"
3) I recommend citing previous work (i.e., Rudd, Aleshire, Zibbell, & Gladden, 2016; Gomes et al., 2018) or providing a more complete rationale when describing the decision to include self-poisoning and homicidal poisoning in drug-overdose death rates along with explicit accidental opioid overdose. The coding utilized by the authors is consistent with previous work,	We have now added the citations and contextualized our decisions in light of recommendations from previous work. Page 10, lines 6-13.

but may at first appear counterintuitive to readers.	
4) I agree with the authors that one limitation with the present analysis is that deaths with more than one contributory code were included in more than one sub-analysis, and should be interpreted with caution. Would it be possible to include secondary analyses to see how robust the findings are when multiple-opioid deaths are excluded vs. included? For example, in the online tool, rather than having to choose between 3 drug types, would there be a way to set this up that the viewer can "select all drugs that apply". In this way, viewers could see how the results change for "prescription opioid only" deaths vs. "heroin and prescription opioid deaths".	We have now added all different combinations of drugs in the interactive app. We also added more detail about the content of the App in the text of the manuscript, including the fact that we also included information o percentage of unspecified codes per CZ. "Detailed results including mortality due to various combinations of opioids, visualizations of the relationships between population metrics and overdose deaths, and percent of unspecified poisoning deaths by CZs were included in an Interactive App available here:…"
5) Another limitation of the present analysis is that 25% of drug-poisoning deaths were coded as unspecified. I appreciate the authors discussing how analyses change before and after imputation. I would also be curious to know whether specific CZ codes or geographic regions were particularly likely to have unspecified drug-poisoning deaths. If so, this may be helpful to note.	In addition to the percent unspecified by CZ (present in the interactive App), we also included additional detail about the distribution of unspecified codes across geographic regions: "The percentage of unspecified codes also varied across regions, which is likely to be related to differences in drug profile. In the first period, the median percent varied from about 19% in the Northeast to 25% in the South. In the third period, the median percent unspecified varied from 3% in the Northeast to 14% in the Midwest. (See Supplemental Table S1 for median and percentile variation)."
6) A very brief explanation of the rationale for using a binary logarithm of the average population in the text would be helpful.	We thank the reviewer for bringing this out, as our use if the binary log (log2), while precise, does not change results vs using a natural logarithm (the most commonly used one for scaling analysis). We reverted back to the natural log and updated description in methods section accordingly.
7) It appears that higher CZ deciles have more variability in the most recent time period relative to the smaller population deciles and earlier years. This may be an interesting discussion point to raise and a direction for future research (for example, what contributes to variability in opioid mortality rates within the high-risk decile, beyond population decline?)	Thank you for pointing this out. We have now added a few sentences highlighting this finding in the discussion: "…we also found great variability in opioid mortality rates across CZs with similar population sizes, particularly in the group of large CZs (deciles 9 and 10) in the last period. This points to the existence of other potential factors in

	these large CZ that are likely to be related to overdose deaths that are beyond population metrics, and is part of a divergence in mortality rates across geographies in the US.[11] Future research should aim to identify potential explanations, being them related to differences in exposure to opioids or differences in policies to reduce harm among users."
8) In the limitations section, the authors state that broader social determinants of health and factors in the local content have a role in the development of substance use disorders. I may recommend changing "substance use disorders" to "overdose" more specifically, as overdose was the focus of the present analysis and because an individual without a substance use disorder can overdose.	Thank you for pointing that out. We have now corrected this issue on page 19, line 16-17.
9) In the following sentence of the limitation sections, the authors generally refer to and recommend harm reduction strategies; more specific recommendations tied to the results of the present study would be beneficial. For example, the authors note that superlinear scaling of opioid deaths was largely driven by synthetic opioids, consistent with rising fentanyl in the drug supply. Increasing access to fentanyl testing strips and naloxone may be actionable harm reduction strategies that the authors could discuss in light of the their findings.	We have now added a few sentences indicating evidence-based actionable strategies to mitigate opioid harm in light of our findings: "In light of these findings, broad public health strategies that increase access to naloxone and medication for opioid use disorders[12,13] and allow for safer use of opioids and other substances, e.g., supervised injection facilities,[14,15] are critical to mitigate opioid harm in the population."
10) Additionally, it is recommended that the authors raise limitations associated with death codes generally, such as varied investigation systems by state, and incomplete toxicology testing in some jurisdictions. While the authors elude to this in the limitations section, a slightly expanded discussion is recommended.	We have expanded our discussion on this issue. We added the paragraph: "We assume that the distribution of unspecified drug codes occurs independently of other factors beyond those we adjusted for in the imputation procedure, including the type of death investigation system, local economic and demographic profile, and geography. While the majority of poisoning deaths during our study period were associated with opioids, deaths involving psychostimulants with abuse potential (e.g., methamphetamines) and cocaine began to increase around 2013.[16] Thus our results about the last period might have overestimated the number of opioid-associated deaths to some extent, although fentanyl was the drug that

	showed the greatest increase during that period (either in isolation or associated with other drugs).[16] Variation in toxicology testing across jurisdictions may also have affected our results. In this scenario, it is possible that the associations observed were at least partially explained by the existence of more comprehensive toxicology testing in larger metropolitan areas of the country, thus revealing a more accurate picture of the types of drugs associated with overdoses in these jurisdictions."
Reviewer 2	
This paper is clear and well written. It presents an analysis to describe the relationship between US urban population size and population growth, and opioid-related mortality. This analysis finds a relationship between urban population decline and higher rates of opioid-related mortality. It does not establish a cause for the relationship. The use of commuting zones is novel, and a good addition to the study of geographic variability in opioid-related mortality. I have not reviewed the statistical methods as this is outside of my area.	Thank you for your comments. Indeed we do not attempt to establish a cause for the relationship. The urban scaling framework is relatively unknown in the field of public health. This paper represents an initial exploration of this topic, but future papers should focus on potential causal mechanisms.
Reviewer 3	
Authors did an excellent job in describing the statistical approach to allow replication.	Thank you for your comment. We appreciate you highlighting this feature of our study.

VERSION 2 – REVIEW

REVIEWER	Jennifer Ellis Johns Hopkins University
REVIEW RETURNED	19-Dec-2021

GENERAL COMMENTS	The authors have addressed all concerns raised by me. I thank them for their efforts, and think this manuscript will make a great contribution to the literature.